

# **Nutritional Biochemistry of the Vitamins**

**SECOND EDITION**

**DAVID A. BENDER**

University College London



**CAMBRIDGE**  
UNIVERSITY PRESS

PUBLISHED BY THE PRESS SYNDICATE OF THE UNIVERSITY OF CAMBRIDGE  
The Pitt Building, Trumpington Street, Cambridge, United Kingdom

CAMBRIDGE UNIVERSITY PRESS

The Edinburgh Building, Cambridge CB2 2RU, UK

40 West 20th Street, New York, NY 10011-4211, USA

477 Williamstown Road, Port Melbourne, VIC 3207, Australia

Ruiz de Alarcón 13, 28014 Madrid, Spain

Dock House, The Waterfront, Cape Town 8001, South Africa

<http://www.cambridge.org>

© David A. Bender 2003

This book is in copyright. Subject to statutory exception  
and to the provisions of relevant collective licensing agreements,  
no reproduction of any part may take place without  
the written permission of Cambridge University Press.

First published 2003

Printed in the United Kingdom at the University Press, Cambridge

*Typefaces* Utopia 9/13 pt. and ITC Symbol      *System*  $\text{\TeX}$  2 $\epsilon$  [TB]

*A catalog record for this book is available from the British Library.*

*Library of Congress Cataloging in Publication Data is available.*

ISBN 0 521 80388 8 hardback

# Contents

List of Figures	<i>page</i> xvii
List of Tables	xxi
Preface	xxiii
<b>1 The Vitamins</b>	<b>1</b>
1.1 Definition and Nomenclature of the Vitamins	2
1.1.1 Methods of Analysis and Units of Activity	6
1.1.2 Biological Availability	8
1.2 Vitamin Requirements and Reference Intakes	10
1.2.1 Criteria of Vitamin Adequacy and the Stages of Development of Deficiency	10
1.2.2 Assessment of Vitamin Nutritional Status	12
1.2.3 Determination of Requirements	17
1.2.3.1 Population Studies of Intake	17
1.2.3.2 Depletion/Repletion Studies	18
1.2.3.3 Replacement of Metabolic Losses	18
1.2.3.4 Studies in Patients Maintained on Total Parenteral Nutrition	19
1.2.4 Reference Intakes of Vitamins	19
1.2.4.1 Adequate Intake	23
1.2.4.2 Reference Intakes for Infants and Children	23
1.2.4.3 Tolerable Upper Levels of Intake	24
1.2.4.4 Reference Intake Figures for Food Labeling	27
<b>2 Vitamin A: Retinoids and Carotenoids</b>	<b>30</b>
2.1 Vitamin A Vitamers and Units of Activity	31
2.1.1 Retinoids	31
2.1.2 Carotenoids	33
2.1.3 International Units and Retinol Equivalents	35

2.2 Absorption and Metabolism of Vitamin A and Carotenoids	35
2.2.1 Absorption and Metabolism of Retinol and Retinoic Acid	35
2.2.1.1 Liver Storage and Release of Retinol	36
2.2.1.2 Metabolism of Retinoic Acid	38
2.2.1.3 Retinoyl Glucuronide and Other Metabolites	39
2.2.2 Absorption and Metabolism of Carotenoids	40
2.2.2.1 Carotene Dioxygenase	41
2.2.2.2 Limited Activity of Carotene Dioxygenase	42
2.2.2.3 The Reaction Specificity of Carotene Dioxygenase	43
2.2.3 Plasma Retinol Binding Protein (RBP)	45
2.2.4 Cellular Retinoid Binding Proteins CRBPs and CRABPs	47
2.3 Metabolic Functions of Vitamin A	49
2.3.1 Retinol and Retinaldehyde in the Visual Cycle	49
2.3.2 Genomic Actions of Retinoic Acid	54
2.3.2.1 Retinoid Receptors and Response Elements	55
2.3.3 Nongenomic Actions of Retinoids	58
2.3.3.1 Retinoylation of Proteins	58
2.3.3.2 Retinoids in Transmembrane Signaling	60
2.4 Vitamin A Deficiency (Xerophthalmia)	61
2.4.1 Assessment of Vitamin A Nutritional Status	64
2.4.1.1 Plasma Concentrations of Retinol and $\beta$ -Carotene	64
2.4.1.2 Plasma Retinol Binding Protein	65
2.4.1.3 The Relative Dose Response (RDR) Test	66
2.4.1.4 Conjunctival Impression Cytology	66
2.5 Vitamin A Requirements and Reference Intakes	66
2.5.1 Toxicity of Vitamin A	68
2.5.1.1 Teratogenicity of Retinoids	70
2.5.2 Pharmacological Uses of Vitamin A, Retinoids, and Carotenoids	71
2.5.2.1 Retinoids in Cancer Prevention and Treatment	71
2.5.2.2 Retinoids in Dermatology	72
2.5.2.3 Carotene	72
<b>3 Vitamin D</b>	77
3.1 Vitamin D Vitamers, Nomenclature, and Units of Activity	78
3.2 Metabolism of Vitamin D	79
3.2.1 Photosynthesis of Cholecalciferol in the Skin	80
3.2.2 Dietary Vitamin D	82
3.2.3 25-Hydroxylation of Cholecalciferol	83
3.2.4 Calcidiol 1 $\alpha$ -Hydroxylase	85
3.2.5 Calcidiol 24-Hydroxylase	85
3.2.6 Inactivation and Excretion of Calcitriol	86
3.2.7 Plasma Vitamin D Binding Protein (Gc-Globulin)	87

3.2.8 Regulation of Vitamin D Metabolism	87
3.2.8.1 Calcitriol	88
3.2.8.2 Parathyroid Hormone	88
3.2.8.3 Calcitonin	88
3.2.8.4 Plasma Concentrations of Calcium and Phosphate	89
3.3 Metabolic Functions of Vitamin D	89
3.3.1 Nuclear Vitamin D Receptors	91
3.3.2 Nongenomic Responses to Vitamin D	92
3.3.3 Stimulation of Intestinal Calcium and Phosphate Absorption	93
3.3.3.1 Induction of Calbindin-D	93
3.3.4 Stimulation of Renal Calcium Reabsorption	94
3.3.5 The Role of Calcitriol in Bone Metabolism	94
3.3.6 Cell Differentiation, Proliferation, and Apoptosis	96
3.3.7 Other Functions of Calcitriol	97
3.3.7.1 Endocrine Glands	98
3.3.7.2 The Immune System	98
3.4 Vitamin D Deficiency – Rickets and Osteomalacia	98
3.4.1 Nonnutritional Rickets and Osteomalacia	99
3.4.2 Vitamin D-Resistant Rickets	100
3.4.3 Osteoporosis	101
3.4.3.1 Glucocorticoid-Induced Osteoporosis	102
3.5 Assessment of Vitamin D Status	103
3.6 Requirements and Reference Intakes	104
3.6.1 Toxicity of Vitamin D	105
3.6.2 Pharmacological Uses of Vitamin D	106
<b>4 Vitamin E: Tocopherols and Tocotrienols</b>	<b>109</b>
4.1 Vitamin E Vitamers and Units of Activity	109
4.2 Metabolism of Vitamin E	113
4.3 Metabolic Functions of Vitamin E	115
4.3.1 Antioxidant Functions of Vitamin E	116
4.3.1.1 Prooxidant Actions of Vitamin E	118
4.3.1.2 Reaction of Tocopherol with Peroxynitrite	119
4.3.2 Nutritional Interactions Between Selenium and Vitamin E	120
4.3.3 Functions of Vitamin E in Cell Signaling	121
4.4 Vitamin E Deficiency	122
4.4.1 Vitamin E Deficiency in Experimental Animals	122
4.4.2 Human Vitamin E Deficiency	125
4.5 Assessment of Vitamin E Nutritional Status	125
4.6 Requirements and Reference Intakes	127
4.6.1 Upper Levels of Intake	128
4.6.2 Pharmacological Uses of Vitamin E	128
4.6.2.1 Vitamin E and Cancer	129
4.6.2.2 Vitamin E and Cardiovascular Disease	129

4.6.2.3 Vitamin E and Cataracts	129
4.6.2.4 Vitamin E and Neurodegenerative Diseases	129
<b>5 Vitamin K</b>	<b>131</b>
5.1 Vitamin K Vitamers	132
5.2 Metabolism of Vitamin K	133
5.2.1 Bacterial Biosynthesis of Menaquinones	135
5.3 The Metabolic Functions of Vitamin K	135
5.3.1 The Vitamin K-Dependent Carboxylase	136
5.3.2 Vitamin K-Dependent Proteins in Blood Clotting	139
5.3.3 Osteocalcin and Matrix Gla Protein	141
5.3.4 Vitamin K-Dependent Proteins in Cell Signaling – Gas6	142
5.4 Vitamin K Deficiency	142
5.4.1 Vitamin K Deficiency Bleeding in Infancy	143
5.5 Assessment of Vitamin K Nutritional Status	143
5.6 Vitamin K Requirements and Reference Intakes	145
5.6.1 Upper Levels of Intake	145
5.6.2 Pharmacological Uses of Vitamin K	146
<b>6 Vitamin B<sub>1</sub> – Thiamin</b>	<b>148</b>
6.1 Thiamin Vitamers and Antagonists	148
6.2 Metabolism of Thiamin	150
6.2.1 Biosynthesis of Thiamin	153
6.3 Metabolic Functions of Thiamin	153
6.3.1 Thiamin Diphosphate in the Oxidative Decarboxylation of Oxoacids	154
6.3.1.1 Regulation of Pyruvate Dehydrogenase Activity	155
6.3.1.2 Thiamin-Responsive Pyruvate Dehydrogenase Deficiency	156
6.3.1.3 2-Oxoglutarate Dehydrogenase and the $\gamma$ -Aminobutyric Acid (GABA) Shunt	156
6.3.1.4 Branched-Chain Oxo-acid Decarboxylase and Maple Syrup Urine Disease	158
6.3.2 Transketolase	159
6.3.3 The Neuronal Function of Thiamin Triphosphate	159
6.4 Thiamin Deficiency	161
6.4.1 Dry Beriberi	161
6.4.2 Wet Beriberi	162
6.4.3 Acute Pernicious (Fulminating) Beriberi – Shoshin Beriberi	162
6.4.4 The Wernicke–Korsakoff Syndrome	163
6.4.5 Effects of Thiamin Deficiency on Carbohydrate Metabolism	164
6.4.6 Effects of Thiamin Deficiency on Neurotransmitters	165
6.4.6.1 Acetylcholine	165
6.4.6.2 5-Hydroxytryptamine	165
6.4.7 Thiaminases and Thiamin Antagonists	166

6.5 Assessment of Thiamin Nutritional Status	167
6.5.1 Urinary Excretion of Thiamin and Thiochrome	167
6.5.2 Blood Concentration of Thiamin	167
6.5.3 Erythrocyte Transketolase Activation	168
6.6 Thiamin Requirements and Reference Intakes	169
6.6.1 Upper Levels of Thiamin Intake	169
6.6.2 Pharmacological Uses of Thiamin	169
<b>7 Vitamin B<sub>2</sub> – Riboflavin</b>	<b>172</b>
7.1 Riboflavin and the Flavin Coenzymes	172
7.2 The Metabolism of Riboflavin	175
7.2.1 Absorption, Tissue Uptake, and Coenzyme Synthesis	175
7.2.2 Riboflavin Binding Protein	177
7.2.3 Riboflavin Homeostasis	178
7.2.4 The Effect of Thyroid Hormones on Riboflavin Metabolism	178
7.2.5 Catabolism and Excretion of Riboflavin	179
7.2.6 Biosynthesis of Riboflavin	181
7.3 Metabolic Functions of Riboflavin	183
7.3.1 The Flavin Coenzymes: FAD and Riboflavin Phosphate	183
7.3.2 Single-Electron-Transferring Flavoproteins	184
7.3.3 Two-Electron-Transferring Flavoprotein Dehydrogenases	185
7.3.4 Nicotinamide Nucleotide Disulfide Oxidoreductases	185
7.3.5 Flavin Oxidases	186
7.3.6 NADPH Oxidase, the Respiratory Burst Oxidase	187
7.3.7 Molybdenum-Containing Flavoprotein Hydroxylases	188
7.3.8 Flavin Mixed-Function Oxidases (Hydroxylases)	189
7.3.9 The Role of Riboflavin in the Cryptochromes	190
7.4 Riboflavin Deficiency	190
7.4.1 Impairment of Lipid Metabolism in Riboflavin Deficiency	191
7.4.2 Resistance to Malaria in Riboflavin Deficiency	192
7.4.3 Secondary Nutrient Deficiencies in Riboflavin Deficiency	193
7.4.4 Iatrogenic Riboflavin Deficiency	194
7.5 Assessment of Riboflavin Nutritional Status	196
7.5.1 Urinary Excretion of Riboflavin	196
7.5.2 Erythrocyte Glutathione Reductase (EGR) Activation Coefficient	197
7.6 Riboflavin Requirements and Reference Intakes	197
7.7 Pharmacological Uses of Riboflavin	198
<b>8 Niacin</b>	<b>200</b>
8.1 Niacin Vitamers and Nomenclature	201
8.2 Niacin Metabolism	203
8.2.1 Digestion and Absorption	203
8.2.1.1 Unavailable Niacin in Cereals	203
8.2.2 Synthesis of the Nicotinamide Nucleotide Coenzymes	203

8.2.3 Catabolism of NAD(P)	205
8.2.4 Urinary Excretion of Niacin Metabolites	206
8.3 The Synthesis of Nicotinamide Nucleotides from Tryptophan	208
8.3.1 Picolinate Carboxylase and Nonenzymic Cyclization to Quinolinic Acid	210
8.3.2 Tryptophan Dioxygenase	211
8.3.2.1 Saturation of Tryptophan Dioxygenase with Its Heme Cofactor	211
8.3.2.2 Induction of Tryptophan Dioxygenase by Glucocorticoid Hormones	211
8.3.2.3 Induction Tryptophan Dioxygenase by Glucagon	212
8.3.2.4 Repression and Inhibition of Tryptophan Dioxygenase by Nicotinamide Nucleotides	212
8.3.3 Kynurenine Hydroxylase and Kynureninase	212
8.3.3.1 Kynurenine Hydroxylase	213
8.3.3.2 Kynureninase	213
8.4 Metabolic Functions of Niacin	214
8.4.1 The Redox Function of NAD(P)	214
8.4.1.1 Use of NAD(P) in Enzyme Assays	215
8.4.2 ADP-Ribosyltransferases	215
8.4.3 Poly(ADP-ribose) Polymerases	217
8.4.4 cADP-Ribose and Nicotinic Acid Adenine Dinucleotide Phosphate (NAADP)	219
8.5 Pellagra – A Disease of Tryptophan and Niacin Deficiency	221
8.5.1 Other Nutrient Deficiencies in the Etiology of Pellagra	222
8.5.2 Possible Pellagragenic Toxins	223
8.5.3 The Pellagragenic Effect of Excess Dietary Leucine	223
8.5.4 Inborn Errors of Tryptophan Metabolism	224
8.5.5 Carcinoid Syndrome	224
8.5.6 Drug-Induced Pellagra	225
8.6 Assessment of Niacin Nutritional Status	225
8.6.1 Tissue and Whole Blood Concentrations of Nicotinamide Nucleotides	226
8.6.2 Urinary Excretion of <i>N</i> <sup>1</sup> -Methyl Nicotinamide and Methyl Pyridone Carboxamide	226
8.7 Niacin Requirements and Reference Intakes	227
8.7.1 Upper Levels of Niacin Intake	228
8.8 Pharmacological Uses of Niacin	229
<b>9 Vitamin B<sub>6</sub></b>	232
9.1 Vitamin B <sub>6</sub> Vitamers and Nomenclature	233
9.2 Metabolism of Vitamin B <sub>6</sub>	234
9.2.1 Muscle Pyridoxal Phosphate	236
9.2.2 Biosynthesis of Vitamin B <sub>6</sub>	236
9.3 Metabolic Functions of Vitamin B <sub>6</sub>	236
9.3.1 Pyridoxal Phosphate in Amino Acid Metabolism	237
9.3.1.1 $\alpha$ -Decarboxylation of Amino Acids	239



9.3.1.2 Racemization of the Amino Acid Substrate	241
9.3.1.3 Transamination of Amino Acids (Aminotransferase Reactions)	241
9.3.1.4 Steps in the Transaminase Reaction	242
9.3.1.5 Transamination Reactions of Other Pyridoxal Phosphate Enzymes	243
9.3.1.6 Transamination and Oxidative Deamination Catalyzed by Dihydroxyphenylalanine (DOPA) Decarboxylase	243
9.3.1.7 Side-Chain Elimination and Replacement Reactions	244
9.3.2 The Role of Pyridoxal Phosphate in Glycogen Phosphorylase	244
9.3.3 The Role of Pyridoxal Phosphate in Steroid Hormone Action and Gene Expression	245
9.4 Vitamin B <sub>6</sub> Deficiency	246
9.4.1 Enzyme Responses to Vitamin B <sub>6</sub> Deficiency	247
9.4.2 Drug-Induced Vitamin B <sub>6</sub> Deficiency	249
9.4.3 Vitamin B <sub>6</sub> Dependency Syndromes	250
9.5 The Assessment of Vitamin B <sub>6</sub> Nutritional Status	250
9.5.1 Plasma Concentrations of Vitamin B <sub>6</sub>	251
9.5.2 Urinary Excretion of Vitamin B <sub>6</sub> and 4-Pyridoxic Acid	251
9.5.3 Coenzyme Saturation of Transaminases	252
9.5.4 The Tryptophan Load Test	252
9.5.4.1 Artifacts in the Tryptophan Load Test Associated with Increased Tryptophan Dioxygenase Activity	253
9.5.4.2 Estrogens and Apparent Vitamin B <sub>6</sub> Nutritional Status	254
9.5.5 The Methionine Load Test	255
9.6 Vitamin B <sub>6</sub> Requirements and Reference Intakes	256
9.6.1 Vitamin B <sub>6</sub> Requirements Estimated from Metabolic Turnover	256
9.6.2 Vitamin B <sub>6</sub> Requirements Estimated from Depletion/Repletion Studies	257
9.6.3 Vitamin B <sub>6</sub> Requirements of Infants	259
9.6.4 Toxicity of Vitamin B <sub>6</sub>	259
9.6.4.1 Upper Levels of Vitamin B <sub>6</sub> Intake	260
9.7 Pharmacological Uses of Vitamin B <sub>6</sub>	261
9.7.1 Vitamin B <sub>6</sub> and Hyperhomocysteinemia	261
9.7.2 Vitamin B <sub>6</sub> and the Premenstrual Syndrome	262
9.7.3 Impaired Glucose Tolerance	262
9.7.4 Vitamin B <sub>6</sub> for Prevention of the Complications of Diabetes Mellitus	263
9.7.5 Vitamin B <sub>6</sub> for the Treatment of Depression	264
9.7.6 Antihypertensive Actions of Vitamin B <sub>6</sub>	264
9.8 Other Carbonyl Catalysts	265
9.8.1 Pyruvoyl Enzymes	266
9.8.2 Pyrroloquinoline Quinone (PQQ) and Tryptophan Tryptophylquinone (TTQ)	266
9.8.3 Quinone Catalysts in Mammalian Enzymes	268

<b>10 Folate and Other Pterins and Vitamin B<sub>12</sub></b>	<b>270</b>
10.1 Folate Vitamers and Dietary Folate Equivalents	271
10.1.1 Dietary Folate Equivalents	271
10.2 Metabolism of Folates	273
10.2.1 Digestion and Absorption of Folates	273
10.2.2 Tissue Uptake and Metabolism of Folate	274
10.2.2.1 Poly- $\gamma$ -glutamylation of Folate	275
10.2.3 Catabolism and Excretion of Folate	276
10.2.4 Biosynthesis of Pterins	276
10.3 Metabolic Functions of Folate	279
10.3.1 Sources of Substituted Folates	279
10.3.1.1 Serine Hydroxymethyltransferase	279
10.3.1.2 Histidine Catabolism	281
10.3.1.3 Other Sources of One-Carbon Substituted Folates	283
10.3.2 Interconversion of Substituted Folates	283
10.3.2.1 Methylene-Tetrahydrofolate Reductase	284
10.3.2.2 Disposal of Surplus One-Carbon Fragments	286
10.3.3 Utilization of One-Carbon Substituted Folates	286
10.3.3.1 Thymidylate Synthetase and Dihydrofolate Reductase	287
10.3.3.2 Dihydrofolate Reductase Inhibitors	288
10.3.3.3 The dUMP Suppression Test	289
10.3.4 The Role of Folate in Methionine Metabolism	289
10.3.4.1 The Methyl Folate Trap Hypothesis	291
10.3.4.2 Hyperhomocysteinemia and Cardiovascular Disease	292
10.4 Tetrahydrobiopterin	294
10.4.1 The Role of Tetrahydrobiopterin in Aromatic Amino Acid Hydroxylases	294
10.4.2 The Role of Tetrahydrobiopterin in Nitric Oxide Synthase	296
10.5 Molybdopterin	297
10.6 Vitamin B <sub>12</sub> Vitamers and Nomenclature	298
10.7 Metabolism of Vitamin B <sub>12</sub>	300
10.7.1 Digestion and Absorption of Vitamin B <sub>12</sub>	300
10.7.2 Plasma Vitamin B <sub>12</sub> Binding Proteins and Tissue Uptake	301
10.7.3 Bacterial Biosynthesis of Vitamin B <sub>12</sub>	303
10.8 Metabolic Functions of Vitamin B <sub>12</sub>	303
10.8.1 Methionine Synthetase	304
10.8.2 Methylmalonyl CoA Mutase	305
10.8.3 Leucine Aminomutase	306
10.9 Deficiency of Folic Acid and Vitamin B <sub>12</sub>	307
10.9.1 Megaloblastic Anemia	308
10.9.2 Pernicious Anemia	308
10.9.3 Neurological Degeneration in Vitamin B <sub>12</sub> Deficiency	309
10.9.4 Folate Deficiency and Neural Tube Defects	310
10.9.5 Folate Deficiency and Cancer Risk	311
10.9.6 Drug-Induced Folate Deficiency	312
10.9.7 Drug-Induced Vitamin B <sub>12</sub> Deficiency	313

10.10 Assessment of Folate and Vitamin B <sub>12</sub> Nutritional Status	313
10.10.1 Plasma and Erythrocyte Concentrations of Folate and Vitamin B <sub>12</sub>	314
10.10.2 The Schilling Test for Vitamin B <sub>12</sub> Absorption	315
10.10.3 Methylmalonic Aciduria and Methylmalonic Acidemia	316
10.10.4 Histidine Metabolism – the FIGLU Test	316
10.10.5 The dUMP Suppression Test	317
10.11 Folate and Vitamin B <sub>12</sub> Requirements and Reference Intakes	318
10.11.1 Folate Requirements	318
10.11.2 Vitamin B <sub>12</sub> Requirements	318
10.11.3 Upper Levels of Folate Intake	319
10.12 Pharmacological Uses of Folate and Vitamin B <sub>12</sub>	321
<b>11 Biotin (Vitamin H)</b>	<b>324</b>
11.1 Metabolism of Biotin	324
11.1.1 Bacterial Synthesis of Biotin	327
11.1.1.1 The Importance of Intestinal Bacterial Synthesis of Biotin	329
11.2 The Metabolic Functions of Biotin	329
11.2.1 The Role of Biotin in Carboxylation Reactions	330
11.2.1.1 Acetyl CoA Carboxylase	330
11.2.1.2 Pyruvate Carboxylase	331
11.2.1.3 Propionyl CoA Carboxylase	331
11.2.1.4 Methylcrotonyl CoA Carboxylase	332
11.2.2 Holocarboxylase Synthetase	332
11.2.2.1 Holocarboxylase Synthetase Deficiency	332
11.2.3 Biotinidase	334
11.2.3.1 Biotinidase Deficiency	335
11.2.4 Enzyme Induction by Biotin	335
11.2.5 Biotin in Regulation of the Cell Cycle	336
11.3 Biotin Deficiency	337
11.3.1 Metabolic Consequences of Biotin Deficiency	338
11.3.1.1 Glucose Homeostasis in Biotin Deficiency	338
11.3.1.2 Fatty Liver and Kidney Syndrome in Biotin-Deficient Chicks	338
11.3.1.3 Cot Death	339
11.3.2 Biotin Deficiency In Pregnancy	340
11.4 Assessment of Biotin Nutritional Status	340
11.5 Biotin Requirements	341
11.6 Avidin	341
<b>12 Pantothenic Acid</b>	<b>345</b>
12.1 Pantothenic Acid Vitamers	345
12.2 Metabolism of Pantothenic Acid	346
12.2.1 The Formation of CoA from Pantothenic Acid	348
12.2.1.1 Metabolic Control of CoA Synthesis	349

12.2.2 Catabolism of CoA	350
12.2.3 The Formation and Turnover of ACP	350
12.2.4 Biosynthesis of Pantothenic Acid	351
12.3 Metabolic Functions of Pantothenic Acid	352
12.4 Pantothenic Acid Deficiency	353
12.4.1 Pantothenic Acid Deficiency in Experimental Animals	353
12.4.2 Human Pantothenic Acid Deficiency – The Burning Foot Syndrome	354
12.5 Assessment of Pantothenic Acid Nutritional Status	355
12.6 Pantothenic Acid Requirements	355
12.7 Pharmacological Uses of Pantothenic Acid	356
<b>13 Vitamin C (Ascorbic Acid)</b>	<b>357</b>
13.1 Vitamin C Vitamers and Nomenclature	358
13.1.1 Assay of Vitamin C	359
13.2 Metabolism of Vitamin C	359
13.2.1 Intestinal Absorption and Secretion of Vitamin C	361
13.2.2 Tissue Uptake of Vitamin C	361
13.2.3 Oxidation and Reduction of Ascorbate	362
13.2.4 Metabolism and Excretion of Ascorbate	363
13.3 Metabolic Functions of Vitamin C	364
13.3.1 Dopamine $\beta$ -Hydroxylase	365
13.3.2 Peptidyl Glycine Hydroxylase (Peptide $\alpha$ -Amidase)	366
13.3.3 2-Oxoglutarate-Linked Iron-Containing Hydroxylases	367
13.3.4 Stimulation of Enzyme Activity by Ascorbate In Vitro	369
13.3.5 The Role of Ascorbate in Iron Absorption and Metabolism	369
13.3.6 Inhibition of Nitrosamine Formation by Ascorbate	370
13.3.7 Pro- and Antioxidant Roles of Ascorbate	371
13.3.7.1 Reduction of the Vitamin E Radical by Ascorbate	371
13.3.8 Ascorbic Acid in Xenobiotic and Cholesterol Metabolism	371
13.4 Vitamin C Deficiency – Scurvy	372
13.4.1 Anemia in Scurvy	373
13.5 Assessment of Vitamin C Status	374
13.5.1 Urinary Excretion of Vitamin C and Saturation Testing	374
13.5.2 Plasma and Leukocyte Concentrations of Ascorbate	374
13.5.3 Markers of DNA Oxidative Damage	376
13.6 Vitamin C Requirements and Reference Intakes	376
13.6.1 The Minimum Requirement for Vitamin C	376
13.6.2 Requirements Estimated from the Plasma and Leukocyte Concentrations of Ascorbate	378
13.6.3 Requirements Estimated from Maintenance of the Body Pool of Ascorbate	378
13.6.4 Higher Recommendations	379
13.6.4.1 The Effect of Smoking on Vitamin C Requirements	380

13.6.5 Safety and Upper Levels of Intake of Vitamin C	380
13.6.5.1 Renal Stones	380
13.6.5.2 False Results in Urine Glucose Testing	381
13.6.5.3 Rebound Scurvy	381
13.6.5.4 Ascorbate and Iron Overload	382
13.7 Pharmacological Uses of Vitamin C	382
13.7.1 Vitamin C in Cancer Prevention and Therapy	382
13.7.2 Vitamin C in Cardiovascular Disease	383
13.7.3 Vitamin C and the Common Cold	383
<b>14 Marginal Compounds and Phytonutrients</b>	<b>385</b>
14.1 Carnitine	385
14.1.1 Biosynthesis and Metabolism of Carnitine	386
14.1.2 The Possible Essentiality of Carnitine	388
14.1.3 Carnitine as an Ergogenic Aid	388
14.2 Choline	389
14.2.1 Biosynthesis and Metabolism of Choline	389
14.2.2 The Possible Essentiality of Choline	391
14.3 Creatine	392
14.4 Inositol	393
14.4.1 Phosphatidylinositol in Transmembrane Signaling	394
14.4.2 The Possible Essentiality of Inositol	394
14.5 Taurine	396
14.5.1 Biosynthesis of Taurine	396
14.5.2 Metabolic Functions of Taurine	398
14.5.2.1 Taurine Conjugation of Bile Acids	398
14.5.2.2 Taurine in the Central Nervous System	398
14.5.2.3 Taurine and Heart Muscle	399
14.5.3 The Possible Essentiality of Taurine	399
14.6 Ubiquinone (Coenzyme Q)	400
14.7 Phytonutrients: Potentially Protective Compounds in Plant Foods	401
14.7.1 Allyl Sulfur Compounds	401
14.7.2 Flavonoids and Polyphenols	402
14.7.3 Glucosinolates	403
14.7.4 Phytoestrogens	404
Bibliography	409
Index	463

## List of Figures

1.1. Derivation of reference intakes of nutrients.	22
1.2. Derivation of requirements or reference intakes for children.	24
1.3. Derivation of reference intake (RDA) and tolerable upper level (UL) for a nutrient.	25
2.1. Major physiologically active retinoids.	32
2.2. Major dietary carotenoids.	34
2.3. Oxidative cleavage of $\beta$ -carotene by carotene dioxygenase.	41
2.4. Potential products arising from enzymic or nonenzymic symmetrical or asymmetric oxidative cleavage of $\beta$ -carotene.	44
2.5. Role of retinol in the visual cycle.	51
2.6. Interactions of all- <i>trans</i> - and 9- <i>cis</i> -retinoic acids (and other active retinoids) with retinoid receptors.	56
2.7. Retinoylation of proteins by retinoyl CoA.	59
2.8. Retinoylation of proteins by 4-hydroxyretinoic acid.	60
3.1. Vitamin D vitamers.	78
3.2. Synthesis of calcitriol from 7-dehydrocholesterol in the skin.	81
3.3. Metabolism of calcitriol to yield calcitriol and 24-hydroxycalcitriol.	84
4.1. Vitamin E vitamers.	110
4.2. Stereochemistry of $\alpha$ -tocopherol.	112
4.3. Reaction of tocopherol with lipid peroxides.	114
4.4. Resonance forms of the vitamin E radicals.	117
4.5. Role of vitamin E as a chain-perpetuating prooxidant.	118
4.6. Reactions of $\alpha$ - and $\gamma$ -tocopherol with peroxynitrite.	119
5.1. Vitamin K vitamers.	132
5.2. Reaction of the vitamin K-dependent carboxylase.	137
5.3. Intrinsic and extrinsic blood clotting cascades.	140
6.1. Thiamin and thiamin analogs.	149
6.2. Reaction of the pyruvate dehydrogenase complex.	154
6.3. GABA shunt as an alternative to $\alpha$ -ketoglutarate dehydrogenase in the citric acid cycle.	157

6.4. Role of transketolase in the pentose phosphate pathway.	160
7.1. Riboflavin, the flavin coenzymes and covalently bound flavins in proteins.	173
7.2. Products of riboflavin metabolism.	180
7.3. Biosynthesis of riboflavin in fungi.	182
7.4. One- and two-electron redox reactions of riboflavin.	184
7.5. Reaction of glutathione peroxidase and glutathione reductase.	186
7.6. Drugs that are structural analogs of riboflavin and may cause deficiency.	195
8.1. Niacin vitamers, nicotinamide and nicotinic acid, and the nicotinamide nucleotide coenzymes.	202
8.2. Synthesis of NAD from nicotinamide, nicotinic acid, and quinolinic acid.	204
8.3. Metabolites of nicotinamide and nicotinic acid.	207
8.4. Pathways of tryptophan metabolism.	209
8.5. Redox function of the nicotinamide nucleotide coenzymes.	215
8.6. Reactions of ADP-ribosyltransferase and poly(ADP-ribose) polymerase.	216
8.7. Reactions catalyzed by ADP ribose cyclase.	220
9.1. Interconversion of the vitamin B <sub>6</sub> vitamers.	233
9.2. Reactions of pyridoxal phosphate-dependent enzymes with amino acids.	238
9.3. Transamination of amino acids.	241
9.4. Tryptophan load test for vitamin B <sub>6</sub> status.	248
9.5. Methionine load test for vitamin B <sub>6</sub> status.	255
9.6. Quinone catalysts.	267
10.1. Folate vitamers.	272
10.2. Biosynthesis of folic acid and tetrahydrobiopterin	277
10.3. One-carbon substituted tetrahydrofolic acid derivatives.	280
10.4. Sources and uses of one-carbon units bound to folate.	281
10.5. Reactions of serine hydroxymethyltransferase and the glycine cleavage system.	281
10.6. Catabolism of histidine – basis of the FIGLU test for folate status.	282
10.7. Reaction of methylene-tetrahydrofolate reductase.	284
10.8. Synthesis of thymidine monophosphate.	287
10.9. Metabolism of methionine.	290
10.10. Role of tetrahydrobiopterin in aromatic amino acid hydroxylases.	295
10.11. Reaction of nitric oxide synthase.	297
10.12. Vitamin B <sub>12</sub> .	299
10.13. Reactions of propionyl CoA carboxylase and methylmalonyl CoA mutase.	305
11.1. Metabolism of biotin.	325
11.2. Biotin metabolites.	326

11.3. Biosynthesis of biotin.	328
12.1. Pantothenic acid and related compounds and coenzyme A.	346
12.2. Biosynthesis of coenzyme A.	347
12.3. Biosynthesis of pantothenic acid.	351
13.1. Vitamin C vitamers.	358
13.2. Biosynthesis of ascorbate.	360
13.3. Redox reactions of ascorbate.	363
13.4. Synthesis of the catecholamines.	365
13.5. Reactions of peptidyl glycine hydroxylase and peptidyl hydroxyglycine $\alpha$ -amidating lyase.	366
13.6. Reaction sequence of prolyl hydroxylase.	368
14.1. Reaction of carnitine acyltransferase.	386
14.2. Biosynthesis of carnitine.	387
14.3. Biosynthesis of choline and acetylcholine.	390
14.4. Catabolism of choline.	391
14.5. Synthesis of creatine.	392
14.6. Formation of inositol trisphosphate and diacylglycerol.	395
14.7. Pathways for the synthesis of taurine from cysteine.	397
14.8. Ubiquinone.	400
14.9. Allyl sulfur compounds allicin and alliin.	402
14.10. Major classes of flavonoids.	403
14.11. Glucosinolates.	404
14.12. Estradiol and the major phytoestrogens.	405



## List of Tables

1.1. The Vitamins	3
1.2. Compounds that Were at One Time Assigned Vitamin Nomenclature, But Are Not Considered to Be Vitamins	5
1.3. Marginal Compounds that Are (Probably) Not Dietary Essentials	6
1.4. Compounds that Are Not Dietary Essentials, But May Have Useful Protective Actions	7
1.5. Reference Nutrient Intakes of Vitamins, U.K., 1991	13
1.6. Population Reference Intakes of Vitamins, European Union, 1993	14
1.7. Recommended Dietary Allowances and Acceptable Intakes for Vitamins, U.S./Canada, 1997–2001	15
1.8. Recommended Nutrient Intakes for Vitamins, FAO/WHO, 2001	16
1.9. Terms that Have Been Used to Describe Reference Intakes of Nutrients	21
1.10. Toxicity of Vitamins: Upper Limits of Habitual Consumption and Tolerable Upper Limits of Intake	26
1.11. Labeling Reference Values for Vitamins	27
2.1. Prevalence of Vitamin A Deficiency among Children under Five	61
2.2. WHO Classification of Xerophthalmia	63
2.3. Biochemical Indices of Vitamin A Status	65
2.4. Reference Intakes of Vitamin A	67
2.5. Prudent Upper Levels of Habitual Intake	69
3.1. Nomenclature of Vitamin D Metabolites	79
3.2. Plasma Concentrations of Vitamin D Metabolites	80
3.3. Genes Regulated by Calcitriol	90
3.4. Plasma Concentrations of Calcidiol, Alkaline Phosphatase, Calcium, and Phosphate as Indices of Nutritional Status	104
3.5. Reference Intakes of Vitamin D	105
4.1. Relative Biological Activity of the Vitamin E Vitamers	111
4.2. Responses of Signs of Vitamin E or Selenium Deficiency to Vitamin E, Selenium, and Synthetic Antioxidants in Experimental Animals	123

4.3. Indices of Vitamin E Nutritional Status	126
5.1. Reference Intakes of Vitamin K	146
6.1. Indices of Thiamin Nutritional Status	168
6.2. Reference Intakes of Thiamin	170
7.1. Tissue Flavins in the Rat	176
7.2. Urinary Excretion of Riboflavin Metabolites	181
7.3. Reoxidation of Reduced Flavins in Flavoprotein Oxidases	187
7.4. Reoxidation of Reduced Flavins in Flavin Mixed-Function Oxidases	190
7.5. Indices of Riboflavin Nutritional Status	196
7.6. Reference Intakes of Riboflavin	198
8.1. Indices of Niacin Nutritional Status	227
8.2. Reference Intakes of Niacin	228
9.1. Pyridoxal Phosphate-Catalyzed Enzyme Reactions of Amino Acids	237
9.2. Amines Formed by Pyridoxal Phosphate-Dependent Decarboxylases	240
9.3. Transamination Products of the Amino Acids	242
9.4. Vitamin B <sub>6</sub> -Responsive Inborn Errors of Metabolism	250
9.5. Indices of Vitamin B <sub>6</sub> Nutritional Status	251
9.6. Reference Intakes of Vitamin B <sub>6</sub>	258
10.1. Adverse Effects of Hyperhomocysteinemia	293
10.2. Indices of Folate and Vitamin B <sub>12</sub> Nutritional Status	315
10.3. Reference Intakes of Folate	319
10.4. Reference Intakes of Vitamin B <sub>12</sub>	320
11.1. Abnormal Urinary Organic Acids in Biotin Deficiency and Multiple Carboxylase Deficiency from Lack of Holo-carboxylase Synthetase or Biotinidase	333
13.1. Vitamin C-Dependent 2-Oxoglutarate-linked Hydroxylases	367
13.2. Plasma and Leukocyte Ascorbate Concentrations as Criteria of Vitamin C Nutritional Status	375
13.3. Reference Intakes of Vitamin C	377

## The Vitamins

The vitamins are a disparate group of compounds; they have little in common either chemically or in their metabolic functions. Nutritionally, they form a cohesive group of organic compounds that are required in the diet in small amounts (micrograms or milligrams per day) for the maintenance of normal health and metabolic integrity. They are thus differentiated from the essential minerals and trace elements (which are inorganic) and from essential amino and fatty acids, which are required in larger amounts.

The discovery of the vitamins began with experiments performed by Hopkins at the beginning of the twentieth century; he fed rats on a defined diet providing the then known nutrients: fats, proteins, carbohydrates, and mineral salts. The animals failed to grow, but the addition of a small amount of milk to the diet both permitted the animals to maintain normal growth and restored growth to the animals that had previously been fed the defined diet. He suggested that milk contained one or more “accessory growth factors” – essential nutrients present in small amounts, because the addition of only a small amount of milk to the diet was sufficient to maintain normal growth and development.

The first of the accessory food factors to be isolated and identified was found to be chemically an amine; therefore, in 1912, Funk coined the term *vitamine*, from the Latin *vita* for “life” and amine, for the prominent chemical reactive group. Although subsequent accessory growth factors were not found to be amines, the name has been retained – with the loss of the final “-e” to avoid chemical confusion. The decision as to whether the word should correctly be pronounced “vitamin” or “veitamin” depends in large part on which system of Latin pronunciation one learned – the *Oxford English Dictionary* permits both.

During the first half of the twentieth century, vitamin deficiency diseases were common in developed and developing countries. At the beginning of the twenty-first century, they are generally rare, although vitamin A deficiency (Section 2.4) is a major public health problem throughout the developing world, and there is evidence of widespread subclinical deficiencies of vitamins B<sub>2</sub> (Section 7.4) and B<sub>6</sub> (Section 9.4). In addition, refugee and displaced populations (some 20 million people according to United Nations estimates in 2001) are at risk of multiple B vitamin deficiencies, because the cereal foods used in emergency rations are not usually fortified with micronutrients [Food and Agriculture Organization/World Health Organization (FAO/WHO, 2001)].

### 1.1 DEFINITION AND NOMENCLATURE OF THE VITAMINS

In addition to systematic chemical nomenclature, the vitamins have an apparently illogical system of accepted trivial names arising from the history of their discovery (Table 1.1). For several vitamins, a number of chemically related compounds show the same biological activity, because they are either converted to the same final active metabolite or have sufficient structural similarity to have the same activity.

Different chemical compounds that show the same biological activity are collectively known as *vitamers*. Where one or more compounds have biological activity, in addition to individual names there is also an approved generic descriptor to be used for all related compounds that show the same biological activity.

When it was realized that milk contained more than one accessory food factor, they were named A (which was lipid-soluble and found in the cream) and B (which was water-soluble and found in the whey). This division into fat- and water-soluble vitamins is still used, although there is little chemical or nutritional reason for this, apart from some similarities in dietary sources of fat-soluble or water-soluble vitamins. Water-soluble derivatives of vitamins A and K and fat-soluble derivatives of several of the B vitamins and vitamin C have been developed for therapeutic use and as food additives.

As the discovery of the vitamins progressed, it was realized that “Factor B” consisted of a number of chemically and physiologically distinct compounds. Before they were identified chemically, they were given a logical series of alphanumeric names: B<sub>1</sub>, B<sub>2</sub>, and so forth. As can be seen from Table 1.2, a number of compounds were assigned vitamin status, and were later shown either not to be vitamins, or to be compounds that had already been identified and given other names.